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 <220> FEATURE:
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<400> SEQUENCE: 61

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 <223> OTHER INFORMATION: Synthetic Polynucleotide

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26

We claim:

1. A double stranded oligonucleotide comprising a sense strand:

5' mG-S-mA-fC-mA-mA-mA-mA-fA-fU-fC-mC-fU-fC-mA-mC-mA-fA-mU-mA-mA-mG-mC-mA-mG-mC-mC-[ademG-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC 3', and

an antisense strand:

5' [MePhosphonate-4O-mU]-S-fU-S-fA-S-mU-fU-mG-fU-fG-mA-fG-mG-fA-mU-fU-mU-fU-mU-mG-fU-mC-S-mG-S-mG 3',

55

wherein:

“-” between nucleosides represent a phosphodiester internucleoside linkage;

“-S-” between nucleosides represent a phosphorothioate internucleoside linkage;

mA represents 2'-O-methyl adenosine ribonucleoside;

mG represents 2'-O-methylguanosine ribonucleoside;

mC represents 2'-O-methyl cytidine ribonucleoside;

mU represents 2'-O-methyluridine ribonucleoside;

fA represents 2'-fluoro-adenosine deoxyribonucleoside;

fG represents 2'-fluoro-guanosine deoxyribonucleoside;

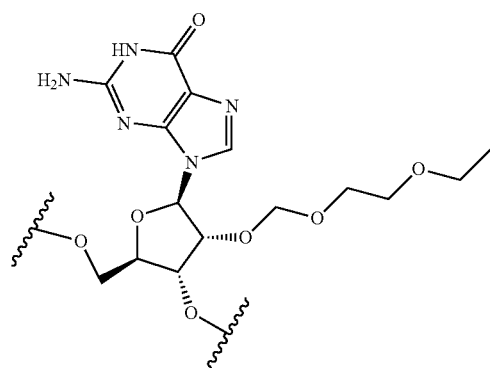
fC represents 2'-fluoro-cytidine deoxyribonucleoside;

60

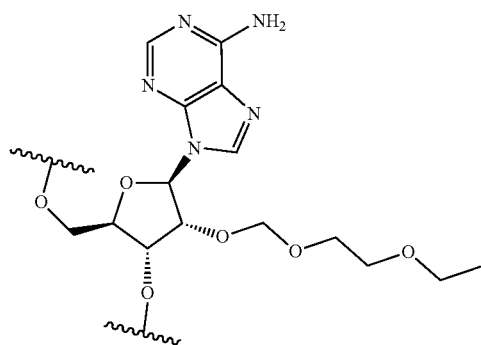
65

79

fU represents 2'-fluoro-uridine deoxyribonucleoside;
[ademG-GalNAc] represents

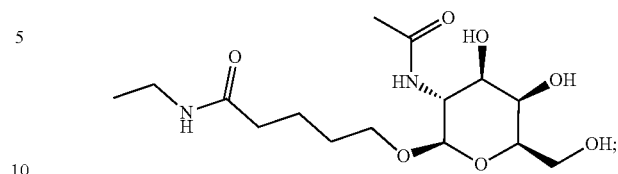


[ademA-GalNAc] represents



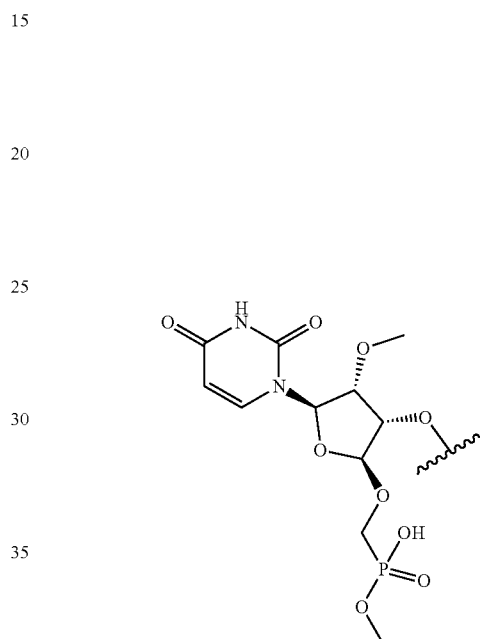
80

-continued



and

[MePhosphonate-4O-mU] represents



2. A sodium salt of a double stranded oligonucleotide comprising a sense strand:

5' mG-S-mA-fC-mA-mA-mA-mA-fA-fU-fC-mC-fU-fC-mA-mC-mA-fA-mU-mA-mA-mG-mC-mA-mG-mC-mC-[ademG-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC 3', and

an antisense strand:

5' [MePhosphonate-4O-mU]-S-fU-S-fA-S-mU-fU-mG-fU-fG-mA-fG-mG-fA-mU-fU-mU-fU-mU-mG-fU-mC-S-mG-S-mG 3',

wherein:

“-” between nucleosides represent a phosphodiester internucleoside linkage;

“-S-” between nucleosides represent a phosphorothioate internucleoside linkage;

mA represents 2'-O-methyl adenosine ribonucleoside;

mG represents 2'-O-methylguanosine ribonucleoside;

mC represents 2'-O-methyl cytidine ribonucleoside;

mU represents 2'-O-methyluridine ribonucleoside;

fA represents 2'-fluoro-adenosine deoxyribonucleoside;

fG represents 2'-fluoro-guanosine deoxyribonucleoside;

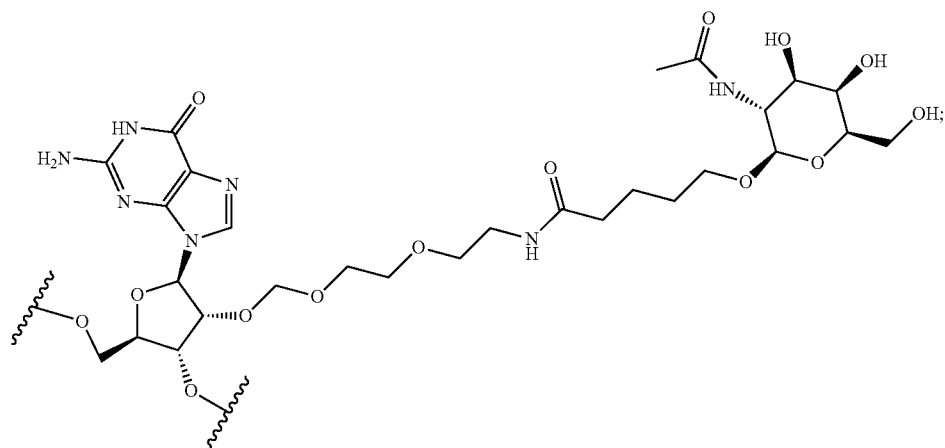
fC represents 2'-fluoro-cytidine deoxyribonucleoside;

fU represents 2'-fluoro-uridine deoxyribonucleoside;

[ademG-GalNAc] represents

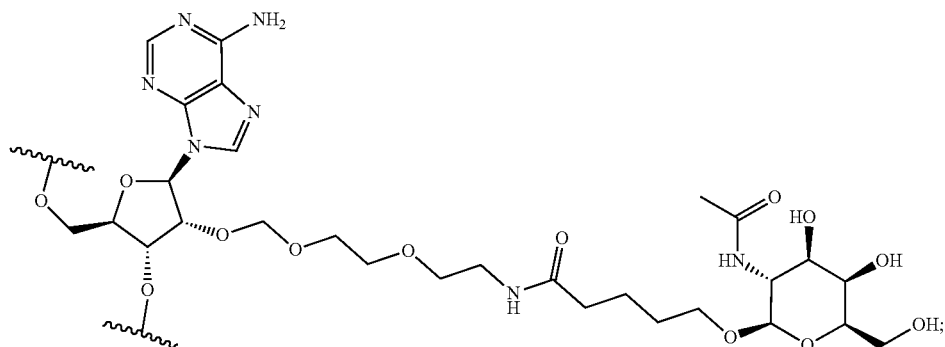
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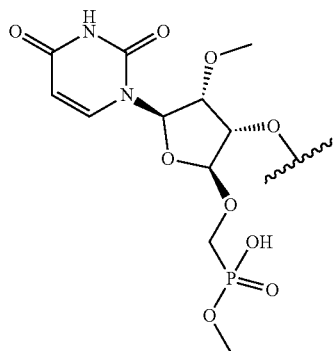
[ademA-GalNAc] represents

20



and

[MePhosphonate-4O-mU] represents



3. A composition comprising a double stranded oligo-
nucleotide, wherein the double stranded oligonucleotide
comprises a sense strand:

45 5' mG-S-mA-fC-mA-mA-mA-mA-fA-fU-fC-mC-fU-fC-
mA-mC-mA-fA-mU-mA-mA-mG-mC-mA-mG-mC-
mC-[ademG-GalNAc]-[ademA-GalNAc]-[ademA-
GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-
mC 3', and

50 an antisense strand:

5' [MePhosphonate-4O-mU]-S-fU-S-fA-S-mU-fU-mG-
fU-fG-mA-fG-mG-fA-mU-fU-mU-fU-mU-mG-fU-
mC-S-mG-S-mG 3',

wherein:

55 “-” between nucleosides represent a phosphodiester inter-
nucleoside linkage;

“-S-” between nucleosides represent a phosphorothioate
internucleoside linkage;

mA represents 2'-O-methyl adenosine ribonucleoside;

60 mG represents 2'-O-methylguanosine ribonucleoside;

mC represents 2'-O-methyl cytidine ribonucleoside;

mU represents 2'-O-methyluridine ribonucleoside;

fA represents 2'-fluoro-adenosine deoxyribonucleoside;

fG represents 2'-fluoro-guanosine deoxyribonucleoside;

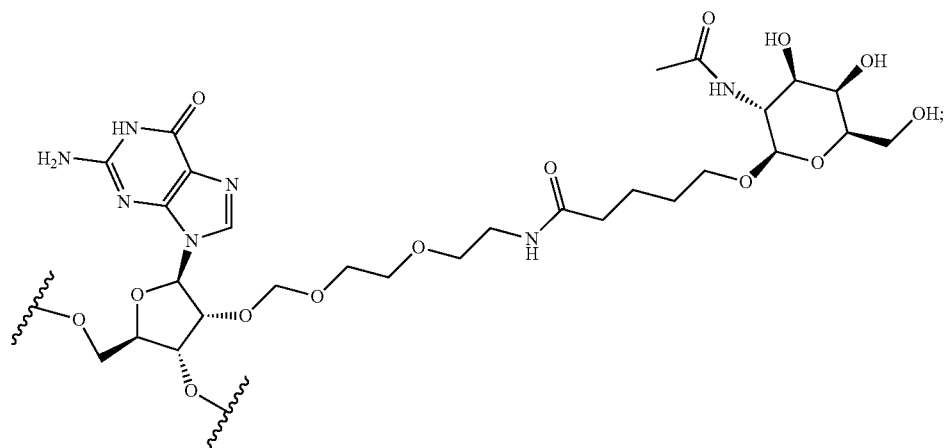
fC represents 2'-fluoro-cytidine deoxyribonucleoside;

fU represents 2'-fluoro-uridine deoxyribonucleoside;

[ademG-GalNAc] represents

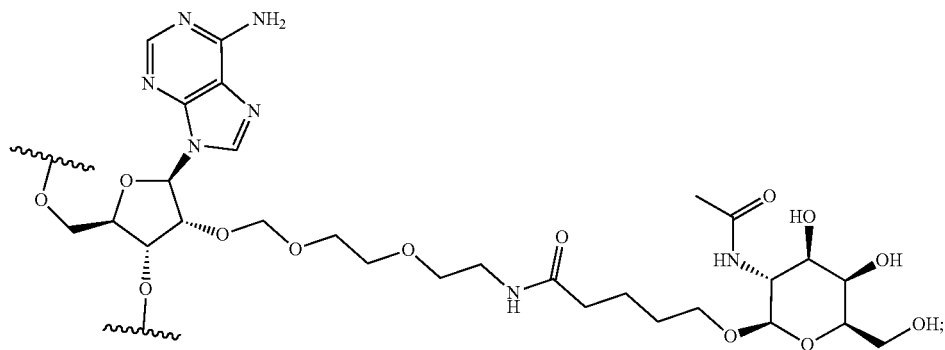
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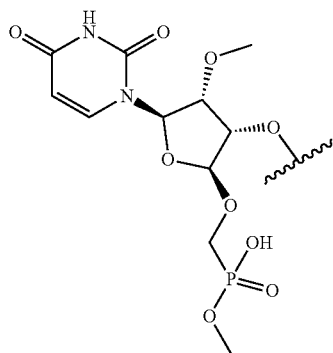
[ademA-GalNAc] represents

20



and

[MePhosphonate-4O-mU] represents



4. The composition of claim 3, further comprising counterions.

5. The composition of claim 4, wherein the counterions are Na⁺ counterions.

6. The composition of claim 3, further comprising a pharmaceutically acceptable carrier.

7. The composition of claim 6, wherein the pharmaceutically acceptable carrier is water.

8. The composition of claim 3, further comprising Na⁺ counterions and water.

9. A method for treating chronic hepatitis B infection in a patient, comprising administering to the patient a composition comprising a double stranded oligonucleotide, wherein the double stranded oligonucleotide comprises a sense strand:

5' mG-S-mA-fC-mA-mA-mA-mA-fA-fU-fC-mC-fU-fC-mA-mC-mA-fA-mU-mA-mA-mG-mC-mA-mG-mC-mC-[ademG-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-[ademA-GalNAc]-mG-mG-mC-mU-mG-mC 3', and

an antisense strand:

5' [MePhosphonate-4O-mU]-S-fU-S-fA-S-mU-fU-mG-fU-fG-mA-fG-mG-fA-mU-fU-mU-fU-mU-mG-fU-mC-S-mG-S-mG 3',

wherein:

"-" between nucleosides represent a phosphodiester internucleoside linkage;

"-S-" between nucleosides represent a phosphorothioate internucleoside linkage;

mA represents 2'-O-methyl adenosine ribonucleoside;

mG represents 2'-O-methylguanosine ribonucleoside;

mC represents 2'-O-methyl cytidine ribonucleoside;

mU represents 2'-O-methyluridine ribonucleoside;

fA represents 2'-fluoro-adenosine deoxyribonucleoside;

fG represents 2'-fluoro-guanosine deoxyribonucleoside;

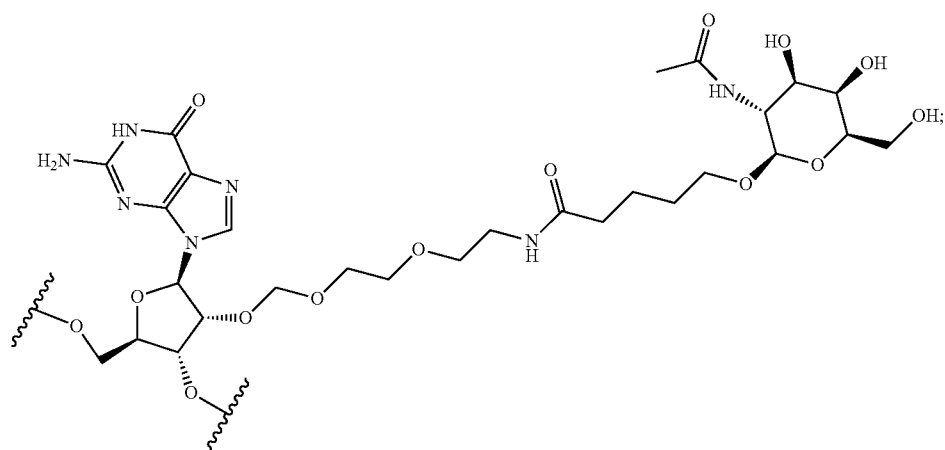
fC represents 2'-fluoro-cytidine deoxyribonucleoside;

fU represents 2'-fluoro-uridine deoxyribonucleoside;

[ademG-GalNAc] represents

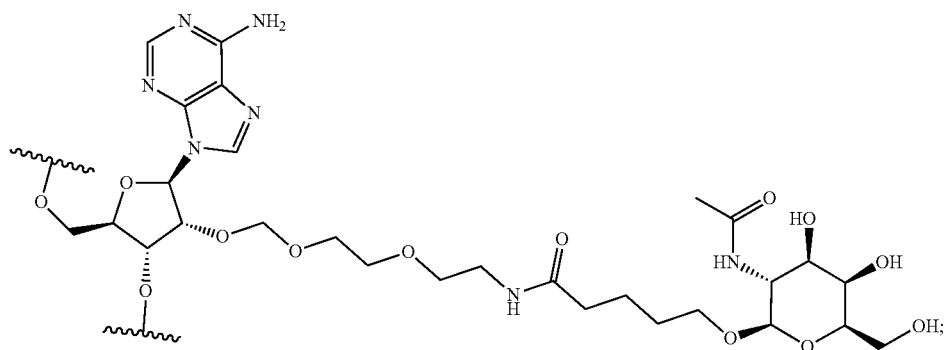
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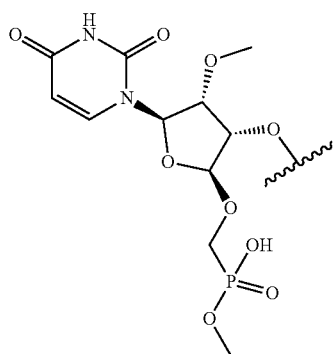
20

[ademA-GalNAc] represents



and

[MePhosphonate-4O-mU] represents



10. The method of claim 9, wherein the composition is administered subcutaneously to the patient.

11. The method of claim 9, wherein the composition further comprises counterions.

12. The method of claim 11, wherein the counterions are Na⁺ counterions.

13. The method of claim 9, wherein the composition further comprises a pharmaceutically acceptable carrier.

14. The method of claim 13, wherein the pharmaceutically acceptable carrier is water.

15. The method of claim 9, wherein the composition further comprises Na⁺ counterions and water.

16. The method of claim 10, wherein the composition further comprises Na⁺ counterions and water.

17. The method of claim 9, wherein the patient is an HBV e-antigen (HbeAg) positive patient.

18. The method of claim 17, wherein the HbeAg positive patient has serum HBV surface antigen (HbsAg) >1000 IU/mL.

19. The method of claim 9, wherein the patient is a HbeAg negative patient.

20. The method of claim 19, wherein the HbeAg negative patient has serum HbsAg >500 IU/mL.

21. The method of claim 9, wherein the patient has serum HBV DNA >20,000 IU/mL.

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